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10/521,064	01/12/2005	Dierk Wieckhusen	VAND-0022-US	6846

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EXAMINER	
KARPINSKI, LUKE E	

ART UNIT	PAPER NUMBER
1616	

NOTIFICATION DATE	DELIVERY MODE
04/28/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTOCommunications@hwdpatents.com

Office Action Summary	Application No.	Applicant(s)	
	10/521,064	WIECKHUSEN ET AL.	
	Examiner	Art Unit	
	LUKE E. KARPINSKI	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 7-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 7-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/01/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt of Amendments to the Claims and Remarks filed 02/01/2008 is acknowledged.

Claims 1-5 and 7-25 are currently pending.

Claim 6 has been canceled by the Applicant.

Withdrawn Claim Objections

The objection of claims 3-5, for not ending in a period, is hereby withdrawn in light of the amendment filed 02/01/2008.

Withdrawn Claim Rejections - 35 USC 112 first paragraph

The rejection of claim 6 under 35 USC 112 first paragraph, is hereby withdrawn in light of the amendment filed 02/01/2008.

Withdrawn Claim Rejections - 35 USC 112 second paragraph

The rejection of claims 1, 2, 7, 8, and 22-25 under 35 USC second paragraph, are hereby withdrawn in light of the Applicants arguments filed 02/01/2008.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining. obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims

2. Determining the scope and contents of the prior art.

3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.SIC. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, and 6-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mutlib et al. and US Publication No. US 2002/0045582 A1 to Margolin et al.

Applicant Claims

Applicant claims an injectable depot formulation comprising crystals of iloperidone or related structures of a specified size range and of different shapes. Applicant also claims said formulation comprising a suitable vehicle as well as excipients well known in the art.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Mutlib et al. teaches the iloperidone structures (introduction) in claim 2 of the instant application for use as a pharmaceutical compound.

Margolin et al. teaches the use of crystals as advantageous for pharmaceutical dosage formulations (paragraph 28) and the administration of crystal formulations through modes such as, parenteral, subcutaneous, and intravenous (paragraph 82). Margolin et al. also teaches that crystals are used for slow-release formulations and that the size and shape of the crystals are important to the dissolution of the crystals and the release of activity (paragraph 28 and 29). Further, Margolin et al. teaches the common excipients and additives that may be added to an injectable crystalline suspension (paragraphs 88(excipients), 102(preservatives), 111(coating agents), 112(sodium carboxymethylcellulose), 119(emulsifiers/solubilizers), 120(stabilizer), 127(humectants),

128(propylene glycol), 131(plasticizers), 132(polyethylene glycol), 135(solvents), 136(propylene glycol), 145(suspending/viscosity agents), 146(carboxymethylcellulose sodium), 147(sweetening agents), 148(mannitol), 150(sodium carboxymethylcellulose), 152(mannitol), 157(tonicity agent), 158(mannitol), and 170(wetting/solubilizing agent)).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Mutlib et al. does not teach injectable iloperidone formulations, nor does Mutlib et al. teach the excipients that are claimed in the instant application. Margolin et al. cures the deficiencies of the teaching of Mutlib et al. by disclosing a general teaching of crystal structures and the advantages of their use in pharmaceutical depot formulations as well as the claimed excipients in injectable solutions.

Finding of Prima Facie Obviousness Rational and Motivation (MPEF §2142-2143)

At the time of the invention iloperidone compounds for pharmaceutical use were well known in the art (see Mutlib et al.). At the time of the invention it was also well known that pharmaceutical formulations in the crystalline form were advantageous to use and that by changing the size or shape of the crystal the dissolution and active ingredient release could be modified (see Margolin et al.). Although Margolin et al. focuses on crystalline forms of proteins, the general properties of crystals vs. amorphous forms would be expected to be the same for protein and small molecule

crystals. It was also known that any common excipients and additives could be added to the injectable crystalline suspension (see Margolin et al.). It is a necessary property of the claimed compound that it can be crystallized. Using the preceding logic, it would have been obvious at the time of the invention to one of ordinary skill in the art to crystallize the iloperidone compound and administer it to patients as an injectable depot formulation. Mutlib et al., with the teachings of Margolin et al., make obvious all of the structures disclosed in the instant claims 1 and 2, the references also make obvious the use of crystals of these structures within an injectable depot formulation, the use of water as a suspension vehicle, adding any excipients known in the art, and using any other form of the drug, such as, salts and hydrates.

In regards to the claim limitations of a size range of the crystals and of different crystal forms, a concentration range, and of different dosages; changing the size, concentration, or dosage is simply seen as routine optimization. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

For these reasons a person of ordinary skill in the art would have a reasonable expectation of success upon modification of the teachings of Mutlib et al. with the teachings of Margolin et al. to use the crystalline form of iloperidone in an injectable solution.

Response to Arguments

Applicant's arguments filed 02/01/2008 have been fully considered but they are not persuasive. The Applicant argues that Mutlib et al. do not disclose an injectable formulation comprising iloperidone and that Mutlib et al. do not disclose any methods of making or using injectable depot formulations.

Upon further consideration of the preamble of claim 1 the examiner has determined that Mutlib et al. do disclose an injectable iloperidone formulation comprising iloperidone or metabolites thereof (page 238, left col. Lines 24-28 and page 239, right col., last paragraph). The examiner points out that the composition does not need to be described as being injectable but must merely be capable of being injected, which the formulation of Mutlib et al. is. The Applicant is correct in stating that Mutlib et al. do not teach any methods of using injectable depot formulations, however, this is of no consequence in light of the fact that the Applicant does not claim any methods of making or using said formulations.

The applicant also argues that not all compounds are found or can be prepared in crystalline form and requests an explanation of the statement of inherency regarding iloperidone in crystal form.

The examiner inadvertently used confusing language in stating the "inherent crystallinity" of the claimed compound. However, the examiner points out that iloperidone is necessarily available in crystalline form and that it would have been obvious to one of ordinary skill in the art to use either the crystalline form or the

amorphous form of the compound. It is also noted by the examiner that a known compound is not patentable simply because it is claimed in crystalline form.

The Applicant repeatedly argues that none of the references teach iloperidone in crystalline form.

The limitation of a compound in the form of a crystal does not make said compound patentably distinct. There is nothing to suggest in the specification that substituting the crystalline form of iloperidone with an amorphous form of the compound would render the formulation inoperable. Further, claim 1 is viewed to read crystals of iloperidone **OR** a metabolite, salt, hydrate, solvate, polymorph, or stereoisomer of iloperidone. The other forms of iloperidone are not necessarily crystals. Since crystals are not required for claim 1 there is no requirement that the prior art teach iloperidone in crystalline form in order to reject claim 1.

The applicant also asserts that it was not predictable that the compound in crystalline form within the claimed size ranges would have the properties described in the instant specification.

The examiner would like to point out that no properties of the compound in crystalline form were claimed and that limitations of the specification are not read into the claims. However, even if said properties were claimed as limitations, the combination of Mutlib et al. and Margolin et al. teach crystals of iloperidone within the claimed size range and said composition would necessarily have all of the same properties as those that may be claimed in the instant application.

The Applicant also argues that Margolin et al. teaches away from the use of non-macromolecules.

Although Margolin et al. teach that macromolecules and typical chemical entities have some differences in properties, the reference does no teach away from using small molecules or crystals thereof. In fact Margolin et al. teach that crystals of small molecules are easier to deal with in regard to stability (paragraph [0022]). Margolin et al. teach that crystals in the micron size range may be combined with other excipients and components, and said formulations utilized for injection purposes. Nowhere in Margolin et al. is it mentioned that crystals of small molecules can not be used, nor does the reference teach away from the use of crystals formed from small molecules. Further, Margolin et al. is used as a secondary reference in a 103 rejection to overcome deficiencies in Mutlib et al. The reference is used for its teachings of crystals and compositions containing said crystals, not for the compounds which make said crystal. The primary reference is used to overcome the compound, the crystallinity of said compound, and the fact that it would have been obvious and routine optimization to use different sizes of crystals.

The applicant finally states that the methods of Margolin et al. for biological macromolecules could not be combined with Mutlib et al.

This argument is moot because methods concerning macromolecules are not mentioned in the rejection; only the use of crystals is mentioned in said rejection.

Claims 3-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mutlib et al. and US Publication No. US 2002/0045582 A1 to Margolin et al., in further view of Corey et al.

Applicant Claims

Applicant claims a depot formulation of two separate stereoisomers of the claimed compound as well as a combination of the stereoisomers.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Mutlib et al, teach the iloperidone structures (introduction) in claim 2 of the instant application for use as a pharmaceutical compound. Corey et al. teaches enatioselective reduction of ketones.

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Mutlib et al. do not teach enantioselective variations of iloperidone structure nor does it teach the crystalline form of the compound. Mutlib et al. also do not teach injectable iloperidone formulations.

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

Corey et al. cures the deficiencies of the teaching of Mutlib et al. by teaching the enantioselective reduction of ketones. At the time of the invention iloperidone compounds for pharmaceutical use were well known in the art (see Mutlib et al.). It was also well known in the art that enantioselective reduction of ketones could be performed (see Corey et al.). It would have been obvious to one of ordinary skill in the art to use this simple enantioselective ketone reduction to synthesize compounds II and III as described in claims 3-5 of the instant application. The ordinary skilled artisan would have been capable of obtaining either or both claimed enantiomers per the teachings of Corey et al. A person of ordinary skill in the art would have a reasonable expectation of success of synthesizing both of the enantiomers. Thus, claims 3-5 are found prima facie obvious over the combined teachings of Mutlib et al. and Corey et al. The combined teachings of Mutlib et al. and Corey et al. make obvious the enantiomers of claims 3 and 4 either together or separate, in crystalline form for use in an injectable depot formulation.

Response to Arguments

Applicant's arguments filed 02/01/2008 have been fully considered but they are not persuasive. The Applicant argues that Corey et al. do not teach the claimed compound, the enantioselective compounds claimed, injectable formulations, or crystals of said compound within the claimed size range.

Corey et al. teach creating enantioselective compounds from ketones. The iloperidone substructure which applicant claims to be enantioselective is a ketone

therefore it would have been obvious to use the teachings of Corey et al. on iloperidone to produce the enantioselective compounds of the claimed invention. Corey et al. do not mention injectable compounds, crystals or size thereof because Corey et al. is used as a secondary reference in order to cure the enantioselective deficiency of Mutlib et al.

The Applicant also argues that Corey et al. do not cure the deficiency of enantiomers of iloperidone in Mutlib et al. because Corey et al. do not teach enantiomers of iloperidone or pure forms thereof.

Corey et al. do not have to teach the entire iloperidone compound in order to teach the modification of said compound, only the sub-structure which is to be modified is required to be taught. Teaching the modification of a specific type of sub-group is a well known practice in the art and one of ordinary skill would have seen that a teaching of Ketone modification could have been used on the ketone sub-group of a larger molecule. Corey et al. also do not have to teach producing a pure form of the structures ,as it is well known in the art to purify compounds after they are synthesized, especially compounds for pharmaceutical use.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Inquiries

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LUKE E. KARPINSKI whose telephone number is (571)270-3501. The examiner can normally be reached on Monday Thursday 9-4 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R. Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LEK

/Johann R. Richter/

Supervisory Patent Examiner, Art Unit 1616